REMARKS

Upon entry of the present amendment, claims 1, 2, 4, 5, 10-22, and 24-29 will be pending. Claims 6, 9, and 23 have been cancelled. Claims 1, 2, 4, 5, and 16-22, and 24-29 have been amended. No new matter has been added.

Claims 1 and 16 have been amended to specify that the two polymers are present in a ratio of from 70:30 to 80:20 by weight. Support for this amendment may be derived from the instant specification as filed, for example, at page 15, second paragraph to page 16, end of first paragraph.

Claims 2 and 17 have been amended to clarify that the stabilizing effect is imparted through at least one of the first and second polymers. Support for this amendment may be found in the original specification, for example, at page 4, first paragraph.

Claims 4, 5, and 18-20 have been amended for clarity, *i.e.*, to clarify that "the polymer allowing a homogenous dispersion" is "said first polymer", and to clarify that the phrase "the polymer allowing enhanced dissolution of the bioactive compound in an aqueous environment" is "said second polymer." No new matter is added.

Applicants gratefully acknowledge the withdrawal of the previous species election and rejoinder of all species for examination.

Claim Objections

Claim 18 has been objected to under 37 C.F.R. § 1.75(c) for alleged failure to further limit the subject matter of a previous claim. Claim 18 has been amended so that it depends from claim 16, rather than from claim 1. Claim 18 has also been amended from clarity, *i.e.*, to clarify that the polymer allowing a homogenous dispersion is the "first polymer." Applicants respectfully submit that claim 18 further limits the subject matter of the claim from which it depends, *i.e.*, by specifying that the first polymer is a copolymer of vinylpyrrolidone and vinylacetate. Accordingly, withdrawal of the objection to claim 18 is respectfully requested.

Claims 17, 19-21, and 23-29 have been objected to under 37 C.F.R. § 1.75 as allegedly being substantial duplicates of claims 2, 4-6, and 9-15. Claims 17, 19-21, and 23-26, 28, and 29 have all been amended to depend from claim 16, rather than from claim 1. Claim 27 has been amended so that it depends from claim 26, rather than from claim 12. At least because claim 16 is different in scope than claim 1, Applicants respectfully submit that the amendments to 17, 19-21, and 23-29 overcome the Office's objection to these claims, and accordingly, that such objection should be withdrawn.

Claim 4 has been objected to under 37 C.F.R. § 1.75 as allegedly being a substantial duplicate of claim 6. Claim 6 has been cancelled. Applicants respectfully submit that the cancellation of claim 6 fully addresses the Office's objection to claim 4.

Claims 19 and 20 have been objected to under 37 C.F.R. § 1.75 as allegedly being substantial duplicates of claims 21 and 22, respectively. Applicants have amended claims 19-22 so that these claims depend from claim 16, rather than from claim 1. Applicants have also amended claims 19 and 20 for clarity; claims 19 and 20 have each been amended to clarify that the polymer allowing enhanced dissolution of the bioactive compound in an aqueous environment is the "second polymer." Applicants respectfully submit that the amendment of claims 19-22 so that those claims depend from claim 16 fully addresses the Office's objection to these claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1 and 16 have been rejected for alleged failure to comply with the written description requirement. Specifically, the Office asserts that the application does not provide "explicit support" for the use of the term "about" in connection with the recited range of ratios for the first and second polymers (10/31/07 Office Action at page 4). Although Applicants do not necessarily agree, at least because explicit support is not required, in order to expedite prosecution, claims 1 and 16 have been amended to remove the term "about" in connection with the recited ratios for the first and second polymers. Applicants respectfully submit that the amendment renders the rejection moot.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1 and 16 have been rejected for alleged indefiniteness because of the failure of those claims to specify whether the recited ratios for the first and second polymers are expressed in terms of weight, volume, or another standard. Claims 1 and 16 have been amended to specify that the recited ratios are "by weight". Applicants respectfully submit that amendment renders the rejection moot.

Claims 2 and 17 have been rejected for alleged indefiniteness with respect to the description of the polymer matrix as comprising a polymer that has a "stabilizing effect" on the bioactive compound. The Office has alleged that it is not clear from the instant specification what "kind or degree of stabilization" is afforded (10/31/07 Office Action at page 6, item 2). Applicants respectfully submit that the "stabilizing effect" is clearly characterized in the instant specification, and accordingly, that one skilled in the art would readily apprehend the subject matter of claims 2 and 17. The specification makes it abundantly clear that stabilization of a drug for purposes of the present invention comprises protection against recrystallization/precipitation, an anti-plasticizing effect, or both. *See*, for example:

- page 12, eight lines from bottom ("Clusters of free drug are not protected and recrystallize. This observation confirms the inadequate stabilization [effect] of a polymer when both phases are not completely mixed. Basic thermodynamics suggests that the occurrence of phase separation will have a major influence of the physical stability of the drug in such dispersions.");
- page 13, twelve lines from bottom (". . . results in the appearance of glassy clusters of drug . . . These clusters experience no protective effect from the surrounding polymer and recrystallization results. It is well described that molecular dispersions and so called solid solutions have higher physical stability due to the antiplasticizing effect and protection against recrystallization from the surrounding polymer . . .");
- page 13, next to last line, to page 14, seven lines from top ("The drug dissolves in all concentrations in the carrier with an increase in Tg because of the antiplasticizing effect of the polymer . . . It is well established that these dispersions will have a much

higher stability . . . because of the total miscibility and therefore ideal situation for the protecting properties of the polymer.");

- page 15, next to last line, to page 16, line 2 ("It is clear that in these dispersions no clusters of pure glassy drug are present, which are able to recrystallize and hence affecting the physical stability and pharmaceutical performance.");
- page 16, lines 10-13 ("Precipitation does not occur because PVPVA64 has a stabilizing effect on itraconazole in solution, which is clearly seen in the dissolution profile of 100% PVPVA64 and well described in literature . . .").

Accordingly, the specification provides clear guidance as to the characteristics of the "stabilizing effect", and Applicants respectfully submit that the rejection of claims 2 and 17 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claims 9 and 23 stand rejected for alleged indefiniteness. The Office alleges that there is insufficient antecedent basis for the term "the bioavailability" as recited in the rejected claims. Although Applicants do not necessarily agree, in order to expedite prosecution, claims 9 and 23 have been canceled. Applicants respectfully submit that amendment renders the rejection moot.

Claim Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, 4-6, and 9-29 have been rejected for alleged obviousness over WO 02/11694 A2 to Rosenberg *et al.* ("the Rosenberg publication") in view of WO 97/44014 to Baert *et al.* ("the Baert publication") or WO 99/33467 to Jung *et al.* ("the Jung publication"). Claims 1, 2, 4-6, and 9-29 have also been rejected for alleged obviousness over the Baert publication in view of *Matsumoto & Zografi, Pharm. Res. 16:11 (1999)* ("the Matsumoto publication") and the Jung publication. However, the cited publications, either alone or in combination, do not teach or suggest solid dispersions comprising the claimed polymers in the claimed ratios.

As Applicants have previously demonstrated, the Office's allegation that the ratio between the first and second polymers "would have been a matter of routine optimization" to one skilled in the art (10/31/07 Office Action at page 15) is improper for several reasons. First, there is no evidence of record demonstrating a recognition that the relative amounts by

weight of polymer is a result-effective variable. M.P.E.P. 2144.05(II)(B) ("[a] particular parameter must first be recognized as a result-effective variable" before the determination of optimum or workable ranges of the variable may be characterized as routine experimentation) (quoting *In re Antonie*, 559 F.2d 618 (CCPA 1977)). The Office's arguments to the contrary are not accurate. For example, the Office alleges that the claimed ratio of the first and second polymeric components (or equivalents theref) have been explicitly disclosed, and cites the Baert publication page 12, last paragraph and the Rosenberg publication on page 7, Examples 1-3 to this effect (*see* 10/31/07 Office Action at page 17, lines 7-10 from top). However, a more fastidious analysis of the cited references reveals that the Office has misinterpreted their respective disclosures.

First, the portion of the Baert publication to which the Office cites does *not* disclose the first and second polymeric components or equivalents thereof in the claimed ratio. The Baert publication discloses a composition in which a combination of "crospolyvidone" and HPMC polymers is used, wherein "crospolyvidone" is present in an amount that is 20.9% by weight of the polymer combination and HPMC is present in an amount that is about 80% by weight of the combination. If it is assumed for the sake of the present discussion that "crospolyvidone" is an equivalent of PVPVA64, then this component may be said to represent the "first polymer" as presently claimed, and HPMC represents the "second polymer" as presently claimed. Thus, the ratio of first polymer to second polymer as disclosed on page 12 of the Baert publication is about 21:80, which does not even closely approach the ratio of first polymer to second polymer recited in claim 1 (*i.e.*, from 70:30 to 80:20), or the ratio recited in claim 16 (70:30). Furthermore, the authors of the Baert publication do not so much as suggest varying the respective percentages of the polymers used on page 12 relative to one another. Thus, the Office's allegation regarding the Baert publication is clearly based on improper reading of that reference and does not support the Office's allegation regarding the alleged recognition of the ratio of the polymeric components as a results-effective variable.

Second, contrary to the Office's allegation, the Rosenberg publication also does not disclose the first and second polymeric components or equivalents thereof in the required ratio. The Rosenberg publication discloses a single example (Example 3) describing the use of a polymer of the first type (*i.e.,* an N-vinylpyrrolidone vinylacetate copolymer) with a

polymer of the second type (hydroxypropylcellulose).[1] The ratio of the first type of polymer to the second type of polymer is 60 w/w:10 w/w, which is outside the claimed ratios. Here, too, the authors do not so much as suggest varying the respective percentages of the polymers used in Example 3, much less revising the percentages in accordance with the claimed invention. The Office's argument to the contrary (*i.e.*, 10/31/07 Office Action at page 17, third line from bottom) is puzzling, as it is abundantly clear that the Rosenberg publication does not disclose an embodiment in which the first and second polymers are present in any other than in a *fixed, unvarying* proportional relationship, as in Example 3. Therefore, the Office's allegation regarding the Rosenberg publication is clearly based on a misinterpretation of that reference as well, and does not support the Office's allegation regarding the alleged recognition of the ratio of the polymeric components as a results-effective variable.

Accordingly, Applicants respectfully submit that the Office has failed to establish the *prima facie* obviousness of the claimed invention.

Moreover, Applicants have also demonstrated that even if a *prima facie* case of obviousness had been presented, the evidence of surprising results that are obtained via the claimed inventions rebuts any such *prima facie* case. However, the Office challenges the persuasiveness of Applicants' arguments (10/31/07 Office Action at page 18). In particular, the Office argues that the demonstration of unexpected results is only relevant for the combination of polymers recited in pending claim 4 (*i.e.*, the combination of a first polymer comprising a copolymer of vinylpyrrolidone and vinylacetate and a second polymer comprising a cationic polymer based on dimethylaminoethyl methacrylate and neutral methacrylic ester), and is only relevant for the combination of the two polymers at a ratio of 70:30 to 80:20 "and not in a ratio of 'about 70:30 to about 80:20' or 'about 70:30'" (10/31/07 Office Action at page 18).

Regarding the latter point, the Office seems to challenge the applicability of the unexpected results to the ratios in view of the inclusion of the term "about", and does not

[1] As shown in Applicants' Reply dated June 21, 2007, Example 1 of the Rosenberg publication uses only a single polymer of the second type that is recited in the claims (*i.e.*, "a ... polymer that has a dissolution profile associated with the creation of a micro-environment enhancing the dissolution of the bioactive compound in an aqueous environment"), and Example 2 uses two polymers of the second type; neither of Examples 1 or 2 describe the use of a polymer of the first type (one which allows a homogenous or molecular dispersion of the bioactive compound in the polymer matrix), and therefore neither are pertinent to the present inquiry.

challenge the points between 70:30 and 80:20.The claims have been amended to delete the term "about", thereby mooting this aspect of the Office's arguments.

While Applicants acknowledge that evidence of nonobviousness must be commensurate in scope with the claims that the evidence is offered to support, where, as here, a claimed genus does not embrace a large number of species and one skilled in the art would recognize that the species concerning which evidence of unexpected results is proffered is representative of the genus in terms of the species' functional characteristics, the nonobviousness of the genus may accurately be said to be supported by a showing of unexpected results with respect to the species. *See In re Kollman*, 595 F.2d 48 (C.C.P.A. 1979) (nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof). Here, the present specification clearly provides that "not only [E]udragit E100 and PVPVA64 can be used but other polymers with the same intrinsic characteristics", *i.e.*, the "improved stability properties" of the first polymer, and the "improved dissolution properties" of the second polymer (both of which effects are discussed in sufficient technical detail throughout the specification), may be used to prepare solid dispersions having the advantageous characteristics of the embodiment disclosed in Figure 13 (*see* page 16, second paragraph). For example, the specification clearly discloses how the correspondence of the dissolution profile of a bioactive drug in Eudragit E100 with the dissolution profile in HPMC indicates that the latter is a functional substitute for the former (*see* page 15, lines 11-17), and one skilled in the art would readily understand that these performance results are applicable to other functional substitutes for Eudragit E100. Likewise, the specification discloses which properties (fast dissolving, forms a molecular dispersion, antiplasticizing effect, complete miscibility, volume additivity, stabilizing effect) give rise to the functional utility of PVPVA4 in the inventive solid dispersions (*see* page 13, second paragraph, to page 14, line 7), and it would be clear to those skilled in the art that other functional substitutes for PVPVA64 would be equally efficacious (*cf.* page 16, second paragraph). Accordingly, one of ordinary skill in the art would be able to determine a trend in the exemplified data that would allow the artisan to reasonably extend the probative value of the unexpected results shown, for example, in Figure 13 of the present application, to the

full scope of each of the instant claims. Applicants therefore respectfully submit that the evidence of surprising results that are obtained via the claimed inventions would rebut any *prima facie* case of obviousness, and the combination of the first and second polymers at a ratio of 70:30 to 80:20 would not have been obvious over the cited art.

For at least these reasons, the rejections of claims 1, 2, 4-6, and 9-29 under § 103(a) should be withdrawn.

Conclusion

Applicants submit that the foregoing represents a *bona fide* attempt to advance the present case to allowance, and that the application is now in condition therefor. Accordingly, an indication of allowability and an early Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-568-3100.

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